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Enhancing cell-free layer thickness by bypass channels in a wall

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ABSTRACT

When blood flows near a wall, red blood cells (RBCs) drift away from the wall and a cell-free layer (CFL) is formed adjacent to the wall. Controlling the CFL thickness is important for preventing adhesion of cells in the design of biomedical devices. In this study, a novel wall configuration with stenoses and bypass channels is proposed to increase the CFL thickness. We found that the presence of bypass channels modified the spatial distribution of cells and substantially increased the CFL downstream of the stenosis. A single-bypass geometry with 5% hematocrit (Hct) blood flow showed a 1.7 μm increase in CFL thickness compared to without the bypass. In the case of three bypass channels, a 3 μm increase in CFL thickness was observed. The CFL enhancement was observed up to 10% Hct, but no significant enhancement of CFL was indicated for 20% Hct blood flow. The mechanism of the CFL enhancement was investigated using a numerical simulation of the flow field. The results showed that the distance between each streamline and the corner of the stenosis compared with size of RBC was important parameter in regulating CFL thickness. These results show the potential of the proposed mechanism to prevent adhesion of cells to biomedical devices.

1. Introduction

Human blood is a multiphase biofluid consisting of red blood cells (RBCs), leukocytes, and platelets in plasma, where RBCs consist of about 99% of the cellular components. The RBC has a biconcave shape with diameter of approximately 8 μm and a thickness of about 2 μm (Korin et al., 2007). When blood flows near a wall, RBCs drift away from the wall, resulting in formation of a cell-free layer (CFL) near the wall (Kim et al., 2009; Maeda, 1996). The CFL can be formed by three mechanisms: inertial, deformation, and size effects. At a sufficiently large particle Reynolds number, inertia-induced lift force is generated in particles and cells (Kersaudy-Kerhoas et al., 2010; Sajeesh and Sen, 2014). When the particle is deformable, deformation-induced lift force appears even at a negligible particle Reynolds number (Goldsmith, 1971; Lominadze and Mchedlishvili, 1999; Pries and Secomb, 2003). Moreover, even for a non-deformable particle at a negligible particle Reynolds number, the particle drifts to the upper streamline when the original streamline comes too close to a wall compared with its size (Wu and Hjort, 2009; Yamada and Seki, 2005; Aoki et al., 2009; Matsuda et al., 2011). The distance between the streamline and the wall can be controlled by the wall configuration, an effect used in this study. Several research groups have designed complex channel geometries to study and control the CFL thickness adjacent to the boundary (Sajeesh and Sen, 2014; Sollier et al., 2009). Faivre et al. (2006), Fujiwara et al. (2009) and Pinho et al. (2013) developed microchannels with constrictions. Ishikawa et al. (2011) and Leble et al. (2011) studied the formation of CFL in microchannel with bifurcation and confluence. Sollier et al. (2010) considerably enhanced the CFL locally by geometric singularities. In these studies, using hydrodynamic forces, the capillary number of RBC deformation was in the range 0.1–10. Thus, both deformation effect and size effect may play roles in the drift of RBCs. Some have attempted to control CFL thickness using inertial lift forces with a high blood-flow rate (Tanaka et al., 2012a; Lee et al., 2014; Jaggi et al., 2007). Most of these studies focused on channel rather than wall geometries. The cell-free layer on the wall is formed gradually from the leading edge of the wall. So it needs some length to be developed and form thick cell-free layer on the wall. However, for biomedical microdevices, such as catheter and stent, that are put inside the vessel, the thick CFL should be developed quickly to decrease the probability of cell adhesion on the wall.

The effects of device material on the surface adsorption and/or degradation of blood cells, such as hemolysis, thrombosis, and coagulation, have been investigated extensively. Biomaterials used in the cardiovascular system can be classified into two major

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classes: (1) metals, such as stainless steel, cobalt chromium alloy, and nickel-titanium alloy; and (2) polymers, such as Nylon, Dacron, Teflon, and polyurethane (Jaganathan et al., 2014; Kutz, 2003). When RBCs are exposed to these biomaterials, some of them may adhere to the surface, leading to hemolysis (Vijayanand et al., 2005). To improve the hemocompatibility of the biomaterial various strategies have been adopted to modify the surface. These techniques may be broadly classified into three major classes: (1) surface modifications, to inhibit blood-material interaction (Shin et al., 2011; Li et al., 2014; Fedel et al., 2009), (2) bioactive coatings, to achieve active anti-thrombotic functions (Hsu, 2001; Murugesan et al., 2008; Lu et al., 2012), and (3) the endothelialization of blood-contacting surfaces (Otsuka et al., 2012; Melchiorri et al., 2012; Schopka et al., 2010). These studies have been successful in improving hemocompatibility; however, fluid dynamic features to improve hemocompatibility by increasing cell-free layer thickness and preventing adhesion of cells to the device surface are lacking. Although platelets interactions with biomaterials are also important, due to the small size of platelets, enhancing platelet-free layer is difficult at the moment. Therefore we focused on enhancing RBC-free layer to decrease RBCs interactions with biomedical microdevices.

Thus, in this study, we propose a novel wall geometry with stenoses and bypass channels to enhance the CFL thickness. We investigated the effects of geometry, number of bypass channels, and Hct on the CFL thickness. The mechanism of the CFL enhancement is discussed with a numerical simulation of the flow field.

2. Materials and methods

2.1. Experimental set-up

The experimental set-up consisted of an inverted microscope (IX71; Olympus, Japan) with an objective lens (magnification, ×20, N.A., 0.75, W.D., 0.17 mm; Olympus, Japan), a high-speed camera (FASTCAM SA3; Photron, Japan), a syringe pump (KD Scientific, Holliston, USA) with a 100 μL syringe (Hamilton, USA) and a thermo plate (Tokai Hit, Japan) to control the temperature at 37 °C. The base system is similar to that in our previous studies (Tanaka et al., 2012b; Yaginuma et al., 2014).

2.2. Working fluids

Three working fluids were used in this study: dextran 40 (DX40; Otsuka Pharmaceutical Co., Ltd., Japan) containing RBCs with hematocrits (Hct) of 5%, 10%, and 20%. The density and viscosity of DX40 at 37 °C were 1.05×10^3 kgm^{-3} and 3.5×10^{-3} Pa s, respectively. The blood was collected from a 37-year-old healthy male volunteer and ethylenediamine tetraacetic acid (EDTA) was added to prevent coagulation. The RBCs were separated from bulk blood by centrifugation and aspiration, and then washed twice with physiological saline (PS). Finally, they were dispersed in PS and preserved at 4 °C prior to the experiment. All procedures in this experiment were carried out in compliance with the Ethics Committee on Clinical Investigation at Graduate School of Engineering, Tohoku University (No. 14A-1).

2.3. Device fabrication

The microfluidic device was manufactured from polydimethyl siloxane (PDMS) using a conventional soft-lithography technique (Lima et al., 2008). It was sealed with a glass slide after treatment of both surfaces with oxygen plasma (PIB-20, Vacuum Device, Japan). The channel geometry and dimensions are shown in Fig. 1. We produced two wall geometries in a single device; one had two stenoses and a single bypass channel in the wall and the other had no bypass channel. The width of each microchannel was 680 μm and the device depth was 20 μm. The small depth was used to facilitate visualization of the CFL thickness. Each stenosis was 200 μm high and 140 μm wide. The width of the space between two stenoses was 140 μm. The bypass channel has a cross section of 20 μm 20 μm and a length of 1100 μm.

2.4. Experimental procedure and Image analysis

Throughout the experiments, the temperature around the device was maintained at 37 °C. Flow rate was controlled by a syringe pump set to release blood at 1 μL/min.

Halogen-illuminated images were taken in the center plane of the device with a resolution of 1024 × 1024 pixels at a frame rate of 125 fps. Recorded images were evaluated using the ImageJ software (NIH) to determine the thickness of the cell-free layer downstream of the stenosis (Abramoff et al., 2004). First, the captured video was converted to a sequence of static images. A typical image obtained is shown in Fig. 2(a). To enhance the image quality and distinguish between RBCs and

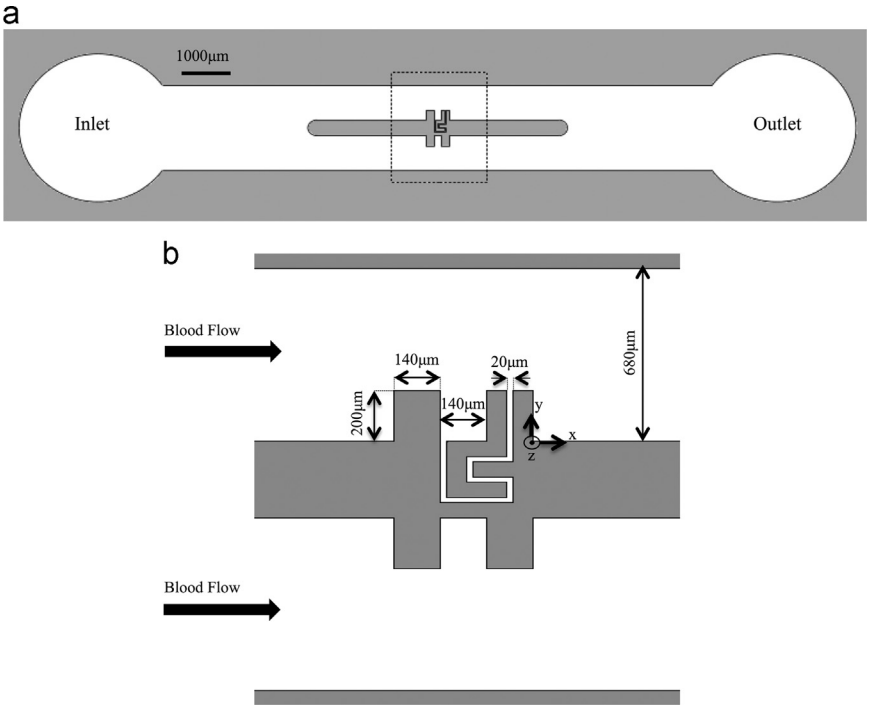

Fig. 1. Channel geometry: (a) Top view of the whole microchannel. The gray sections are composed of PDMS and the white sections are channels with a depth of 20 μm. (b) The detailed geometry of the dashed square region in (a). The flow is from left to right. The geometry is symmetrical between the upper and bottom half, with the exception of the bypass channel. The bypass channel has a cross section of 20 × 20 μm and a length of 1100 μm.

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